UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/961,227	09/20/2001	Alan Upshall	STEM1170-1	4074

28213 7590 01/27/2004

GRAY CARY WARE & FREIDENRICH LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/961,227	UPSHALL ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-19,21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 12/8/03
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7/16/03
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-24 are pending.

Election/Restrictions

Applicant's election of Group III (claims 20 and 22-24) filed on 11/3/03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-19 and 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. filed on 11/3/03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence

or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to using an expression vector comprising a nucleic acid encoding TGF-alpha or a biologically fragment thereof in a method of cell proliferative disorder gene therapy. The invention lies in the field of gene therapy for cell proliferative disorder using transforming growth factor alpha (TGF-alpha).

The art of record teaches that TGF-alpha is a principal molecule in the normal and neoplastic development of several organs. See Lu et al., Proc Assoc Am Physicians, 1996, 108: 165-72; Humphreys et al., Oncogene, 2000, 19: 1085-91; Greten et al., Pancreatology, 2001, 1: 363-8.

Furthermore, the art of record teaches that administration to mouse skin a DNA construct expressing human TGF-alpha resulted in epidermal acanthosis and hypergranulosis. The art of record also teaches using TGF-alpha antisense gene therapy to inhibit head and neck squamous cell carcinoma growth in vivo (Endo et al., Gene Therapy, Vol. 7, pages 1906-1914, 2000). The art of record further teaches blocking the binding site for EGF and TGF-alpha with an anti-receptor antibody is effective for anti-cancer therapy (Mendelsohn, Endocrine-Related Cancer, Vol. 8, pages 3-9, 2001).

Furthermore, and with respect to claims directed to any cancer gene therapy method and directed to any treatment of a subject; the state of the art, exemplified by Anderson et al., *Nature*, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any gene therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

Furthermore, the art for record cancer gene therapy as exemplified by Vile et al., *Gene Therapy*, Vol. 7, pp. 3, 2000 supported the problems with gene therapy taught by Anderson and Verma. Vile teaches:

> To date, cancer gene therapy trials have variously used the three most common vectors (plasmid, retrovirus, and adenovirus). However, except for the situation where tumor/immune cells are manipulated ex vivo, there will be a clear preference in the coming years for the use of adenoviral vector for in vivo delivery to tumors. Dominant (10^{11} p.f.u./ml) compared with other vectors. The initial rationale of the use of C-type retroviral vectors to target exclusively dividing tumor cells on the background of a quiescent tissue is being gradually superseded by the realization that human tumors generally cycle much more slowly than the rodent cell lines on which the strategy was based.
>
> However, even the highest titer system is clearly not high enough yet to cure even local tumors. Therefore, there is a clear need to explore and exploit, a range of alternative options. Other systems, such as AAV and HSV, are already well developed for use in other gene therapy contexts and may be valuable in certain conditions within the cancer area.
>
> The development of replication vectors for cancer gene therapy is the inevitable consequence of data from the early clinical trials. So far, a substantial therapeutic gap still exists between the overlap of the efficacy provided by, on the other hand, the potency of the therapeutic gene(s) and on the other, the efficiency of gene delivery

provided by the vector. Only when these two 'therapeutic domains' approach each other will clinical efficacy result.

Therefore, in view of the art of record at the time the application was filed, cancer gene therapy using TGF alpha was considered unpredictable.

In view of the In Re Wands Factors, the specification fails to provide sufficient guidance or factual evidence for one skilled in the art to practice the claimed method in claims 20 and 22-24 without an undue amount of experimentation. The specification does not provide a working example of the claimed cancer gene therapy method. Furthermore, the specification teaches administering gfa50 (TGF-alpha polypeptide), cisplatinum or gfa and cisplatinum to a xenograft tumor on a nude mouse. Delivering a protein to a tumor is different than delivering a nucleic acid encoding a protein to a tumor cell because expressing TGF-alpha polypeptide outside a tumor cell is not the same as delivering a nucleic acid encoding a TGF-alpha to a tumor cell and expressing TGF-alpha inside the tumor cell. In addition, Figure 1 and 3 are directed to gfa50 and cisplatinum efficacy in human epidermal cancer model. However, the examiner cannot determine the results for gfa50 set forth in Figure 1 because the symbol (▪) used for gfa50 is displayed twice. Figure 3 has the same problem as Figure 1. Thus, the as-filed specification fails to teach using a vector comprising a nucleic acid encoding TGF-alpha to treat any cell proliferative disorder in a subject. Furthermore, the art of record teaches that one skilled in the art would want to inhibit expression of TGF-alpha in a subject to treat a cell proliferative disorder in the subject and not over-express TGF-alpha in the subject to treat the cell proliferative disorder. See Lu (*supra*), Mendelsohn (*supra*), Endo (*supra*). In view of the art of record, the results from the examples in the specification would not lead one skilled in the art to

use a vector comprising a nucleic acid sequence encoding a TGF-alpha protein to treat a cell proliferative disorder in a subject. The art of record further teaches that, "the spontaneous behavior of human tumors is somewhat different for that of malignant cells *in vitro*, and from that of experimental tumors in animal models" (Gomez-Navarro et al., *European Journal of Cancer*, Vol. 35, pp. 867-885, 1999). In view of the reasons set forth above, the as-filed specification fails to provide sufficient guidance and/or factual evidence for one skilled in the art to reasonably extrapolate from the specification to practicing the claimed method in claims 20 and 22-24. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed vectors generate a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record for using a vector expressing TGF-alpha to treat a cell proliferative disorder in a subject.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made do not provide sufficient guidance and/or evidence for one skilled in the art to practice the claimed invention without an undue amount of experimentation. Given that gene therapy wherein any carrier is employed to correct a cell proliferative disorder in any subject using a vector comprising a nucleotide sequence encoding TGF-alpha was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any gene delivery vector cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based

on the applicants' disclosure and the art of record teaching that overexpression of TGF-alpha is associated with cancer in an animal.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, SPE - Art Unit 1635, can be reached at (571) 272-0760.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

Brian Whiteman
Patent Examiner, Group 1635

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER